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The N-7 regioisomer of 2-chloro-2′-deoxyadenosine: synthesis, crystal structure, conformation, and stability

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Abstract

The nucleoside 6-amino-2-chloro-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-7*H*-purine **7** is readily accessible in two steps from 2,6-dichloropurine. The crystal structure of this unusual nucleoside reveals a bifurcated intramolecular hydrogen bond from the amino group to the O-5′ with a weaker branch to the O-4′ which imposes a *syn* glycosidic torsion angle: $\chi = 67.0°$. Semi-empirical calculations using AM1 parameters and optimisation of atomic co-ordinates derived from the crystal structure of **7** suggest that the molecule can adopt either *anti* or *syn* conformations with a slight preference for *anti* by 0.4 kcal mol^{-1} in heat of formation (ΔH_f). NOE experiments in $(CD_3)_2SO$ solution support the theoretical results indicating the presence of both *syn* and *anti* conformations and that the *anti* population is marginally favoured. The antileukaemic agent 2-chloro-2′-deoxyadenosine (**6**), the N-9 regioisomer of **7**, was shown to be 9.6 kcal mol^{-1} more stable than **7**. The increased stability of **6** over **7** seems attributable mainly to the relative stability of the aglycon tautomers **8** and **9**, the energy difference between these being 6.7 kcal mol^{-1} in favour of the 9*H* tautomer **8**. Likewise, removal of the 2-chloro substituent has little effect on the tautomerism.

Keywords: N-7 nucleoside; X-ray structure; Semi-empirical; Conformation; NOE

1. Introduction

There is much interest in the development of synthetic antigene oligonucleotides as chemotherapeutic agents [1–3]. Antigene molecules capable of forming stable triplexes

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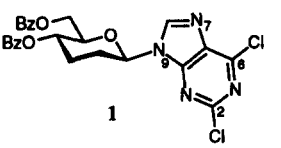
with target gene sequences through Hoogsteen hydrogen bonds [4] allow potential control of gene expression. The pattern of Hoogsteen hydrogen bonding depends on the *syn / anti* conformations of the purine nucleotide components around the glycosidic bond: χ O-4′–C-1′–N-9–C-4 [5]. Our interest in nucleosides for antigene applications has prompted an investigation of the structure and conformation of N-7 purine nucleosides. Much is already known about the chemical and biochemical properties of N-9 purine nucleosides [6], whereas relatively little attention has been directed toward N-7 regioisomers [7] despite their potential antigene applications. We have identified 6-amino-2-chloro-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-7*H*-purine (**7**), the N-7 regioisomer of the known antileukaemic agent 2-chloro-2′-deoxyadenosine (**6**), as a useful intermediate for the synthesis of N-7 nucleosides which may be incorporated into potential antigene oligonucleotides. Here we describe a convenient two-step synthesis of **7** and examine the conformation and stability of this unusual nucleoside by analysis of its crystal structure, semi-empirical molecular orbital calculations, and NOE difference spectroscopy.

2. Results and discussion

Chemical synthesis of purine nucleosides can attach the component ring systems at both the N-9 and N-7 of the nucleobase [8,9]. The problem of regioselectivity is compounded in the synthesis of 2′-deoxyribonucleosides from 2′-deoxy sugars since both β and α nucleoside products may be formed. In the *ribo* series there is stereocontrol from 2′-OAc or 2′-OBz groups neighbouring the anomeric centre in that case. A direct glycosylation method [10] was investigated for the preparation of **7** since coupling of the sodium salt of 2,6-dichloropurine to 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl chloride (**2**) [11] was reported to yield only β nucleosides [12] with apparently no contaminating α anomers. Furthermore, the synthetic versatility of nucleosides containing 2,6-dichloropurine is generally well-established [10,12]. Such synthetic versatility was exemplified recently by the construction of hexose-DNA molecules [13,14] containing isoguanine, xanthine, and 2,6-diaminopurine [15], from the same starting material **1** [16,17]. Regioselective displacement at C-6 of **1** occurs readily using amine and alkoxide nucleophiles whereas elevated temperature and longer reaction time are required to substitute the C-2 position.



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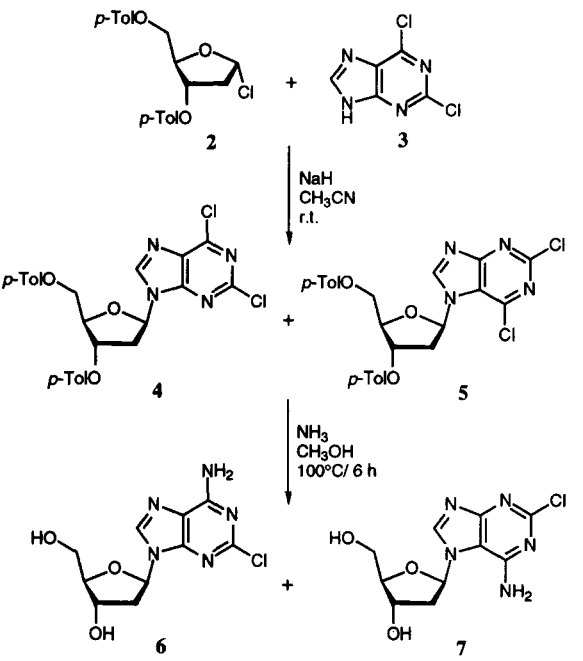
Replacement of the hexose sugar at N-9 by pentose [12] or alkylcarboxylates [18] has little effect on the relative reactivities of C-6 and C-2. 2-Chloro-2′-deoxyadenosine (**6**) is readily accessible from **4** after regioselective displacement at C-6 by ammonia [12]. We



Scheme 1.

reasoned that the regiochemistry displayed by **6** might be mirrored in the N-7 isomer **7**. The sodium salt of 2,6-dichloropurine **3** was glycosylated using the chloro sugar **2** to form **4** and **5** shown in Scheme 1. The crude product mixture contained **4** and **5** in a ratio of 4:1 as determined by ^{1}H NMR spectroscopy. After filtration and evaporation of the solvent, ammonolysis of the crude reaction mixture gave **6** and **7**. Separation by flash column chromatography, followed by recrystallisation from methanol, gave the analytically pure nucleosides **6** and **7** in isolated yields of 34% and 9%, respectively, over two steps. No C-2 substituted adducts were detected in these experiments. Nucleoside **6** was isolated as an amorphous solid whereas the N-7 regioisomer **7** gave crystals suitable for X-ray analysis.

The relevant crystallographic data for **7** are given in Table 1. The structure was solved by direct methods implemented in the program MULTAN [19]. Co-ordinates and anisotropic displacement parameters were refined with SHELXL [20] for all non-hydrogen atoms, along with co-ordinates and isotropic temperature factors for all hydrogen atoms except that attached to O-3′, which was placed in a calculated position to optimise an intermolecular hydrogen bond. The final co-ordinates of the C, N, and O atoms are listed in Table 2. [1] The view (ORTEP [21]) of a molecule of **7** given in Fig. 1 shows clearly that the structure is an N-7 nucleoside where the anomeric centre C-1′ of the

[1] Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Table 1
Crystallographic data for nucleoside 7 [a]

Formula	$C_{10}H_{12}C1N_5O_3$
Mol wt	285.70
Mp (°C)	> 300
Crystal dimensions (mm)	0.6 × 0.35 × 0.25
Space group	$P2_1$
Cell parameters (Å)	
a	7.276(3)
b	9.084(4)
c	9.270(5)
β(°)	104.00(4)
Volume *V* (Å^3)	594.5
Z	2
F(000)	296.0
Calculated density D_x (g cm^{-3})	1.596
λ (Mo$K\alpha$) (Å)	0.71069
μ (cm^{-1})	3.4
2θ range (deg)	2–26
Reflections collected	2519
Symmetry independent reflections	2324
Observed reflections with $F > 4\sigma(F)$	2214
Number of refined parameters	216
Ratio of valued reflections to parameters	10.8
Final residual factors (all data)	
R	0.055
R_w	0.136
Goodness of fit *S*	1.034
Largest difference peak (e Å^{-3})	0.50
Largest difference hole (e Å^{-3})	−0.57
Diffractometer	Enraf–Nonius CAD4

[a] Standard deviations in parentheses.

sugar ring is attached to N-7 of the purine base. There is a bifurcated intramolecular hydrogen bond with the amino group at C-6 of the aglycon as donor and the O-5′ of the sugar ring as acceptor with N · · · O 2.803 Å and N-H · · · O 148°. The additional branch, although weaker, is to the O-4′ of the sugar ring as the acceptor with N · · · O 3.145 Å and N-H · · · O 135°. Formation of this bond imposes a *syn* glycosidic torsion angle: χ O-4′–C-1–N-7–C-5 = 67.0°. There is a *gauche–gauche* disposition of O-5′ with respect to the sugar ring; thus O-4′–C-4′–C-5′–O-5′ and C-3′–C-4′–C-5′–O-5′ are −60.6° and 57.8°, respectively. With pseudorotation parameters $P = 110°$ and $t_m = 38.6°$, the sugar ring attains one of the less common conformations where C-1′ is *exo* and O-4′ is *endo*.

Like purine nucleosides, pyrimidine nucleosides can adopt the *syn* conformation as well as the *anti* conformation despite the possibility of steric clashes between the O-2 and O-5′ centres. The anti-HIV agent AZT [22,23] and the protected analogue ATAZT [24] both adopt the *anti* orientation in the crystal structure, whereas 4-thiouridine is *syn* [25]. Since the energy barrier between *syn* and *anti* conformational states of the more

Table 2
Fractional positional parameters [a] of Cl ($\times 10^5$), C, N, and O (all $\times 10^4$) atoms, and the equivalent isotropic temperature factors U_{eq} [b] ($\times 10^4$) for **7**

Atom	x/a	y/b	z/c	U_{eq}
C1-2	−18473(10)	15964(10)	24336(8)	441(3)
O-3′	10156(3)	501(3)	9019(3)	464(6)
O-4′	6430(3)	−1729(2)	7241(2)	322(5)
O-5′	4966(3)	−971(3)	9597(2)	475(6)
N-1	725(4)	800(3)	4726(3)	325(5)
N-3	1223(4)	205(3)	2331(3)	321(5)
N-6	2810(4)	249(3)	6948(3)	347(6)
N-7	5469(3)	−794(3)	4860(2)	291(5)
N-9	4249(4)	−869(3)	2397(3)	352(5)
C-2	296(4)	755(3)	3247(3)	313(6)
C-4	2956(4)	−293(3)	3063(3)	299(6)
C-5	3639(4)	−237(3)	4605(3)	282(6)
C-6	2430(4)	249(3)	5478(3)	288(6)
C-8	5725(5)	−1134(3)	3505(3)	318(6)
C-1′	6974(4)	−803(3)	6205(3)	283(5)
C-2′	7407(4)	670(4)	6963(3)	332(6)
C-3′	8163(4)	271(4)	8593(3)	335(6)
C-4′	7667(4)	−1367(4)	8674(3)	303(6)
C-5′	6648(5)	−1785(4)	9837(3)	380(7)

[a] Standard deviations in parentheses.
[b] $U_{eq} = (1/3)\ \Sigma_i \Sigma_j a_i^* a_j^* \mathbf{a}_i \mathbf{a}_j$.

Table 3
Semi-empirical (AM1) calculations on **6**, **7**, and aglycons **8–11**

Structure	χ (°)	P (°) [c]	t_m (°) [c]	ΔH_f (kcal mol^{-1})
6 *syn*	82.0 [a]	11.2	16.2	−49.4
6 *anti*	−102.9 [a]	−14.3	16.7	−50.8
7 *syn*	56.6 [b]	87.4	27.9	−40.8
7 *anti*	−161.8 [b]	17.1	16.6	−41.2
dA *syn*	−21.3 [a]	−72.5	21.8	−46.5
dA *anti*	−177.8 [a]	−92.2	23.8	−46.4
dA′ *syn*	−17.0 [a]	−56.4	20.4	−45.1
dA′ *anti*	175.2 [a]	−72.5	17.1	−44.4
8				86.8
9				93.5
10				83.8
11				90.8

[a] O-4′–C-1′–N-9–C-4.
[b] O-4′–C-1′–N-7–C-5.
[c] Pseudorotation angle $P = \tan^{-1}(B/A)$ and amplitude $t_m = \sqrt{(A^2 + B^2)}$ were calculated according to the procedure of Sundaralingam and co-workers [34,35] where

$$A = 0.4 \sum_{i=1}^{5} \theta_i' \cos[144°(i-1)] \text{ and}$$

$$B = -0.4 \sum_{i=1}^{5} \theta_i' \sin[144°(i-1)],$$

with the torsion angles θ_i' beginning with θ_1' = C-1′–C-2′–C-3′–C-4′ and proceeding consecutively around the sugar ring with atom numbers increasing.

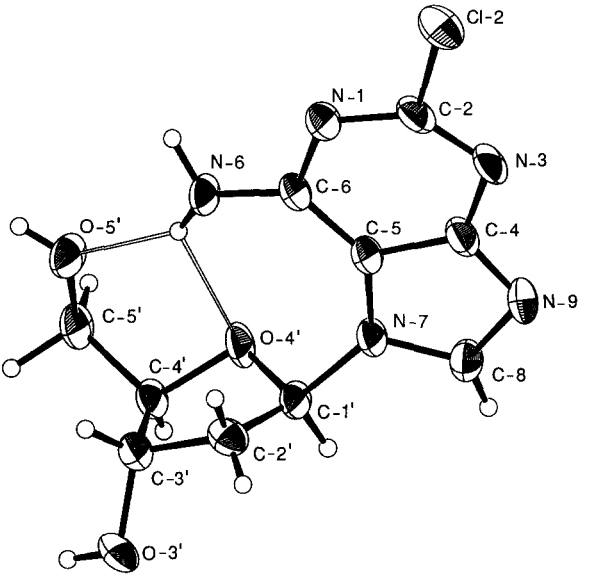
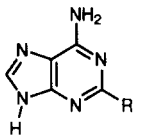
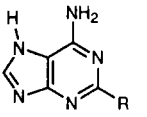


Fig. 1. ORTEP plot of nucleoside **7** showing atom numbering.

common purine and pyrimidine nucleosides is generally small (ca. 6 kcal mol^{-1} [26,27]) a dynamic equilibrium between these conformational states is likely in most cases. The *syn / anti* equilibrium involving 2′-deoxyguanosine residues is important during the conformational change from right-handed B-DNA to left-handed Z-DNA [28,29]. The pattern of Hoogsteen hydrogen bonding interaction between an antigene oligonucleotide and a duplex DNA sequence depends to some extent on the *syn / anti* dispositions of the nucleoside components around the glycosidic bond [1]. It was therefore of interest to examine the conformation of **7** in order to determine whether the molecule could indeed adopt another conformation in addition to the imposed *syn* conformation evident in the crystal structure (Fig. 1).

Semi-empirical molecular orbital calculations with AM1 parameters were performed on **7** using starting co-ordinates derived from the crystal structure. Calculated heats of formation (ΔH_f) for **7** in both *syn* and *anti* conformations are given in Table 3. The regioisomer **6** was generated by moving the point of sugar attachment to N-9. Following optimisation, the *anti* conformers of **6** and **7** were generated by 180° rotation about the glycosidic bond and reoptimisation. The same theoretical procedures were used to investigate the relative stability of *syn* and *anti* conformers of 2′-deoxyadenosine (**dA**). From crystal structures of the anhydrous material and the monohydrate, two independent molecules **dA** [30] and **dA′** [31] were obtained, both *anti*. After full optimisation with AM1 parameters, the *syn* conformers were generated by 180° rotation of the glycosidic torsion angles and similarly optimised (Table 3). Where optimisation with MOPAC [32] did not satisfy the convergence criterion (gradient norm 0.1), the process was concluded with GAMESS [33]. The C-1′ *exo*, O-4′*endo* sugar pucker evident in the crystal structure of **7** became less pronounced on energy minimisation and changed from the twist to a

8 R = Cl; 9*H*-2-chloroadenine **9** R = Cl; 7*H*-2-chloroadenine
10 R = H; 9*H*-adenine **11** R = H; 7*H*-adenine

Fig. 2. Structural formulae of aglycon tautomers **8**–**11**.

pure O-4′-*endo* envelope conformation. The existence of both *syn* and *anti* orientations for **7** is predicted with the *anti* conformation marginally preferred since ΔH_f for the *anti* conformation is only 0.4 kcal mol^{-1} more negative than that for the *syn* conformation. It is not uncommon for AM1 calculations to underestimate hydrogen bond energies but the results of NOE experiments described below agree well with the calculations for **7** with its bifurcated intramolecular hydrogen bond. The calculated heats of formation for **6** *syn* and **6** *anti* are given for comparison in Table 3 and suggest that this N-9 regioisomer, like **7**, can adopt either *syn* or *anti* conformations since the energy difference is only 1.4 kcal mol^{-1} in favour of the *anti* conformation. For both structures **dA** and **dA′** the *syn* arrangement is marginally (< 1 kcal mol^{-1}) more stable than the *anti* (Table 3).

Compound **6** is more stable than compound **7** by 9.6 kcal mol^{-1} according to the values for each *anti* conformation. The increased stability of **6** over **7** seems mainly attributable to the relative stability of the 9*H*- and 7*H*-adenine tautomers **8** and **9** (Fig. 2). Even with the sugar moiety removed, the energy difference between the 2-chloroadenine aglycons **8** and **9** remains 6.7 kcal mol^{-1} in favour of the 9*H* tautomer **8** (Table 3). Likewise, removal of the 2-chloro substituent has little effect on tautomerism since the energy difference between the 9*H* and 7*H* tautomers of adenine, **10** and **11**, remains 7.0 kcal mol^{-1} in favour of the 9*H* tautomer **10**.

The solution conformation of a series of nucleoside analogues has been investigated using one-dimensional ^1H NOE difference spectroscopy [36]. Irradiation of H-8 of purine nucleosides can result in positive NOE values at H-1′, H-2′, and H-3′, depending on the *syn* or *anti* conformation adopted in solution. In order to assess how the solution conformation might compare with that predicted by the theoretical calculations, we carried out NOE measurements on **7** according to the literature method [36]. NOE data for **6** and **7** from NMR experiments are given in Table 4 together with literature values for **dA** and **6** for comparison. Percentage values for *syn* and *anti* populations were estimated assuming a maximum NOE of 11.3% for complete population of the ideal *syn* conformation ($40° < \chi < 50°$) and a maximum NOE of 9.5% for complete population of the ideal *anti* conformation ($-140° < \chi < -150°$) [36]. The NOE data reported in Table 4 support the results of the theoretical calculations. In solution, the N-9 isomer **6** has a slight preference for the *anti* orientation (53% *anti*). This compares favourably with a previously reported value (59% *anti* [6]) although the authors suggest, on this basis, that the *syn* conformation is preferred by **6**. The literature NOE data for **dA** (53% *syn*) agree with the preference for the *syn* orientation predicted by calculation (Table 3). In solution, the N-7 nucleoside **7** is less discriminating between *syn* and *anti* conforma-

Table 4
NOE data (%) of purine 2′-deoxyribonucleosides **6**, **7**, and **dA** upon irradiation of CH-8 [a]

	6	**7**	**dA** [36]	**6** [6]
CH-2′ + CH-3′	5.0 (53% [b])	4.7 (49% [b])	2.7 (28% [b])	5.6 (59% [b])
CH-1′	4.0 (35% [c])	5.4 (48% [c])	6.0 (53% [c])	4.7 (42% [c])

[a] Measured in $(CD_3)_2SO$ at 25°C.
[b] Estimated *anti* population assuming an ideal *anti* conformation has a maximum NOE of 9.5% [36].
[c] Estimated *syn* population assuming an ideal *syn* conformation has a maximum NOE of 11.3% [36].

tions with the *anti* conformation being only marginally preferred which agrees with that predicted by the theoretical calculations. The increased *syn* population exhibited by **7** compared with **6** is due, at least in part, to the contribution from intramolecular hydrogen bonding between the amino group of the aglycon and the O-5′ and O-4′ of the sugar ring. Chemical transformation of the C-2 position of **7** to give nucleoside derivatives suitable for incorporation into potential antigene oligonucleotides is currently under investigation.

3. Experimental

General methods.—NMR spectra were recorded on a Bruker AC250 spectrometer at ^1H (250.1 MHz) and ^{13}C (62.9 MHz). Positive chemical shifts are downfield of the tetramethylsilane reference. NOE experiments were carried out as described previously [36]. Mass spectra were recorded on a Quatro II instrument using positive ion electrospray. Infrared spectra were recorded on a Mattson Galaxy 2020 FT-IR Spectrophotometer. Ultraviolet spectra were recorded using a Unicam PU8730 Spectrophotometer. Melting points were measured on a Gallenkamp Electrothermal Digital apparatus and are uncorrected. Flash column chromatography was performed using Sorbsil C60 silica gel. TLC was performed using plastic-backed Kieselgel 60 plates containing a fluorescent indicator. Spots were visualised under 254 nm UV light and with the aid of ethanolic anisaldehyde–H_2SO_4. Elemental analyses were performed by Butterworth Laboratories, Middlesex. Acetonitrile was distilled from calcium hydride before use.

*6-Amino-2-chloro-9-(2-deoxy-β-*D-erythro*-pentofuranosyl)-9*H*-purine* (**6**) *and 6-amino-2-chloro-7-(2-deoxy-β-*D-erythro*-pentofuranosyl)-7*H*-purine* (**7**).—A mixture of 2,6-dichloropurine (**3**) (2.0 g, 10.58 mmol) and NaH (60% in mineral oil, 0.448 g, 11.21 mmol) in dry MeCN (100 mL) was stirred at room temperature under Ar for 1.5 h. 2-Deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl chloride (**2**) [11] (4.11 g, 10.58 mmol) was added in four equal portions during 30 min. After a further 22 h, the product mixture was filtered through Celite. Evaporation of the solvent gave a mixture of **4** and **5** in a 4:1 ratio (^1H NMR). A saturated solution of methanolic ammonia (70 mL) was added to the crude product and the mixture was heated in a bomb at 100°C for 6 h. The solution was evaporated and the residue purified on a silica gel column (4 × 23 cm) using 9:1 CH_2Cl_2–MeOH as eluant. The N-9 isomer **6** was eluted first, followed by compound **7**. Compound **6** was recrystallised from MeOH; yield, 1.03 g, 34% over two

steps; mp > 300°C (lit. [12] > 300°C); TLC (4:1 CH_2Cl_2–MeOH): R_f 0.36; UV (95% EtOH): λ_{max} 265 nm (ϵ 14800); IR (KBr disc): υ_{max} 3550, 3470, 3400, 3240, 2937, 1637, 1619, 1577, 1303, 1230, and 1057 cm^{-1}; ^1H NMR [$(CD_3)_2SO$]: δ 2.26 (ddd, 1 H, H-2′a), 2.63 (ddd, 1 H, H-2′b), 3.54 (ddd, 2 H, H-5′a,5′b), 3.84 (ddd, 1 H, H-4′), 4.37 (ddd, 1 H, H-3′), 4.98 (t, 1 H, J 5.8 Hz, OH-5′), 5.33 (d, 1 H, J 4.2 Hz, OH-3′), 6.25 (t, 1 H, $J_{1',2'a} = J_{1',2'b} = 6.4$ Hz, H-1′), 7.85 (s, 2 H, NH_2), 8.35 (s, 1 H, H-8); ^{13}C NMR [$(CD_3)_2SO$]: δ 39.8 (C-2′), 62.1 (C-5′), 71.2 (C-3′), 84.0 (C-1′), 88.4 (C-4′), 118.6 (C-5), 140.4 (C-8), 150.5 (C-4), 153.5 (C-2), 157.2 (C-6); mass spectrum (electrospray): m/z (I_r) 288 ($M + H^+$, 31%), 286 ($M + H^+$, 93%), 172 (33%), 170 (100%), 149 (8%), 117 (16%), 85 (11%). Anal. Calcd for $C_{10}H_{12}ClN_5O_3$: C, 42.0; H, 4.2; Cl, 12.4; N, 24.5. Found: C, 42.2; H, 4.0; Cl, 12.5; N, 24.2.

The N-7 isomer **7** was isolated and recrystallised from MeOH; yield, 0.21 g, 9% over two steps; mp > 300°C; TLC (4:1 CH_2Cl_2–MeOH): R_f 0.23; UV (95% EtOH): λ_{max} 277 nm (ϵ 7400); IR (KBr disc): υ_{max} 3411, 3346, 3306, 3112, 2910, 1645, 1594, 1550, 1378, 1226, and 941 cm^{-1}; ^1H NMR [$(CD_3)_2SO$]: δ 2.33 (ddd, 1 H, H-2′a), 2.42 (ddd, 1 H, H-2′b), 3.54 (ddd, 2 H, H-5′a,5′b), 3.87 (ddd, 1 H, H-4′), 4.37 (ddd, 1 H, H-3′), 5.18 (t, 1 H, J 5.8 Hz, OH-5′), 5.40 (d, 1 H, J 4.2 Hz, OH-3′), 6.28 (t, 1 H, $J_{1',2'a} = J_{1',2'b} = 6.4$ Hz, H-1′), 7.48 (s, 2 H, NH_2), 8.55 (s, 1 H, H-8); ^{13}C NMR [$(CD_3)_2SO$]: δ 41.3 (C-2′), 60.6 (C-5′), 69.5 (C-3′), 85.9 (C-1′), 88.1 (C-4′), 109.8 (C-5), 145.0 (C-8), 152.9 (C-6 or C-2), 153.5 (C-6 or C-2), 162.3 (C-4); mass spectrum (electrospray): m/z (I_r) 288 ($M + H^+$, 8%), 286 ($M + H^+$, 25%), 172 (13%), 170 (39%), 149 (70%), 117 (59%), 85 (100%). Anal. Calcd for $C_{10}H_{12}ClN_5O_3$: C, 42.0; H, 4.2; Cl, 12.4; N, 24.5. Found: C, 42.3; H, 4.0; Cl, 12.5; N, 24.2.

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